REMARKS

Reconsideration of the above-identified application in view of the following remarks is respectfully requested.

Claims 1-19 are pending in this case. Claims 9-19 have been withdrawn from further consideration as being drawn to non-elected inventions. Claims 1-8 have been examined on merits. Claims 1-8 have been rejected. Claims 1 and 8 have now been amended. New claims 20-27 have now been added.

35 U.S.C. §112 First Paragraph Rejections

The Examiner has rejected claims 1-8 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement and/or as containing subject matter which has not been described in the specification in such a way as to enable one skilled in the art to which it pertains, or which is most nearly connected, to make and/or use the invention, and has recited the factors that have been considered in this respect. Claims 1 and 8 have been amended.

Specifically, in one particular, the Examiner has stated that claims contain subject matter, "the variable R_3" of the formula of the claims (phosphatidyl choline, phosphatidyl serine, etc.), which was not described in the specification in such as way as to reasonable convey to one skilled in the relevant art that the inventor, at the time the application was filed, has possession of the claimed invention.

More specifically, the Examiner has stated that the limitation of the variable "R_3" in the working examples is preferably a phosphocholine moiety and that no other limitation is found in the specification of the instant application. The Examiner has further stated that based on the unpredictable nature of the invention, the state of the prior art and the breadth of the claims, one skilled in the art could not perform the claimed invention without undue experimentation.

The Examiner has suggested to replace the term "phosphatidyl choline" with the term "phosphocholine"; to replace the term "phosphatidyl ethanolamine" with the term "phosphoethanolamine"; to replace the term "phosphatidyl serine" with the term "phosphoserine"; to replace the term "phosphatidyl cardiolipin" with the term "phosphocardiolipin"; and to replace the term "phosphatidyl inositol" with the term "phosphoinositol", to thereby obviate the rejection.

Claim 1 has now been amended according to the Examiner's suggestion, to recite the term "phosphocholine" instead of "phosphatidyl choline"; the term "phosphoethanolamine" instead of "phosphatidyl ethanolamine"; the term "phosphoserine" instead of "phosphatidyl serine"; the term "phosphocardiolipin" instead of "phosphatidyl cardiolipin"; and the term "phosphoinositol" instead of "phosphatidyl inositol".

In another particular, the Examiner has stated that that the specification, while being enabling for methods of treating atherosclerosis using the compounds as claimed in amended claim 1, does not reasonably provide enablement for a method of **preventing** atherosclerosis. The Examiner has suggested to eliminate the limitation "preventing and/or" from the claims.

Claim 1 has now been amended according to the Examiner's suggestion, to no longer recite the controversial term "preventing".

In still another particular, the Examiner has stated that the specification does not reasonably provide enablement for HMGCoA reductase inhibitors other than statins and has suggested amending the claims so as to incorporate the limitation of HMGCoA reductase inhibitors, i.e., statins.

Claim 8 has now been amended according to the Examiner's suggestion, to no longer recite the phrase "HMGCoA reductase inhibitors" and to recite the term "statins" instead.

Applicants therefore believe to have overcome the Examiner's rejections in this respect.

35 U.S.C. §102(b) Rejections

The Examiner has rejected claims 1-8 under 35 U.S.C. §102(b) as being anticipated by Kern et al. (Biochimica et Biophysica Acta (1998) 1394(1), 33-42; Junius et al. (U.S. Patent No. 5,091,527); Aono et al. (JP 63054386); Nitta et al. (Journal of Leukocyte Biology (1984), 36(4), 493-504; Macpherson et al. (Journal of Lipid Mediators (1992), 5(1), 49-59; Wang et al. (Chemistry and Physics of Lipids (1990), 55(3), 265-73; Karasawa et al. (Journal of Biochemistry (1991), 110(5), 683-7; Smal et al. (Molecular Immunology (1989), 26(8), 711-19); and Berchtold. (Chemistry and Physics of Lipids (1981), 28 (1), 55-60. The Examiner's rejections are respectfully traversed.

Specifically, the Examiner has stated that while the Applicant claims methods of use, using compounds having a general Formula, the above-cited references each teaches compounds that anticipate the claimed compounds.

Applicant wishes to point out in this respect that the claims before the Examiner are directed to a method of treating atherosclerosis and related disorders (as cited in claim 1 of the instant application), which is effected by the administration of a compound having the general Formula I. The claimed compounds are oxidized LDL derivatives, which were found to induce immune tolerance to oxidized LDL and thus serve as potential therapeutic agents for treating or preventing atherogenesis and associated disorders.

The Examiner's attention is directed in this respect, for example, to Examples II-VII of the instant application, where the efficacy of the claimed compounds in inducing immune tolerance to oxidized LDL and in inhibiting atherogenesis is demonstrated.

Applicant wished to further point out that while some of the cited references may teach compounds that are embraced by general Formula I, none of these references teaches or remotely suggest the use of these compounds for the treatment of atherogenesis and/or associated disease.

In fact, Macpherson et al., Kern et al., Aono et al., Wang et al., Smal et al. and Karasawa et al. all teach Platelet activation factor (PAF) analogs, which are aimed at mimicking the activity of PAF in inducing platelet aggregation.

Nitta et al. teach studies conducted on the phospholipase A_2 activity of Fcγ2b receptors of thioglycollate-elicited murine peritoneal macrophages.

Berchtold discloses a glycerophosphocholine oxidized derivative, which is aimed to be used in column chromatography.

Gunius et al. teach substrates of phospholipase A, which are designed so as to enable optical determination of phospholipases.

It is therefore clear that since none of the cited references teaches a method of treating atherogenesis and related disorders, and further since the claimed invention is directed to a method of treating atherogenesis and related disorders, the claimed invention is not anticipated by these references.

It is therefore the Applicant's opinion that claims 1-8 are allowable.

35 U.S.C. §103(a) Rejection

The Examiner has rejected claims 1-8 under 35 U.S.C. §103(a) as being unpatentable over Smal et al. The Examiner's rejection is respectfully traversed. Claim 1 has been amended. New claims 20-27 have been added.

Specifically, the Examiner has stated that Smal et al. disclose two PAF analogs that are related to hypertension and bronchoconstriction, which, according to the Examiner's statement, are considered heart diseases. The Examiner has further stated that one would be motivated to employ the compound and inherent teachings of Smal et al. in the treatment of a cardiovascular disease with a compound that falls within the scope of claims 1-8 of the instant application, whereby the motivation to practice the invention derives from the expectation that the instant claimed compounds would possess similar activities (treating cardiovascular disease) as the known Smal et al. compounds.

The Examiner has also stated under the Item "Determination of the difference between the prior art and the claims (MPEP §2141.2)", that the difference between the instant claims and Smal et al. is that the instant variable Z represents aldehyde or carboxylic acid, while Smal et al. represents aldehyde at the same position.

Applicant wishes to point out in this respect that the Examiner's rejection is not clear. More specifically, Applicant believes that if the Examiner finds that both the claimed compound and its claimed use (treating cardiovascular disease) are taught by Smal et al., the claimed invention should be rejected under 35 U.S.C. §102(b) as being anticipated by Smal et al.

In addition, Applicant wishes to further point out that, contrary to the Examiner's statement, Smal et al. do not teach the use of the compounds taught therein for treating **hypertension** but rather teaches the effect of PAF analogs on **hypotension** and more particularly, on **renal blood pressure** (see, for example, page 711, line 8 of the reference).

Applicant wishes to note in this respect that while according to the Examiner's statement, hypotension and bronchoconstriction are considered as heart diseases, the present art does not provide an established rationale for such a statement.

In fact, it is well known in the art that hypotension typically reduces the risk to develop a heart disease. Bronchoconstriction is a phenomenon associated with

asthma, whereby asthma is known as an inflammatory disease and by no means is related to heart diseases.

It is therefore clear that by teaching a method of treating hypotension and particularly renal blood pressure, and/or bronchoconstriction, Smal et al. fail to teach or remotely suggest a method of treating a heart disease.

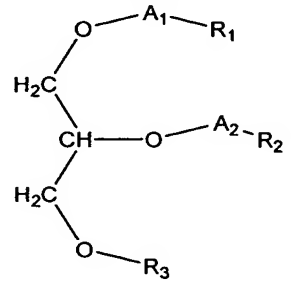
Notwithstanding the above, and in order to expedite prosecution, Applicant has chosen to amend claim 1, to no longer recite a cardiovascular disease as a condition that is treatable by the claims method.

Applicant believes that amended independent claim 1, as well as claims 2-8, which directly or indirectly depend therefrom, are not anticipated nor rendered obvious by Smal et al. and are therefore allowable.

New claims

New claims 20-27 have now been added. New claims 20-27 pertain to a method of treating atherosclerosis and related diseases, which is effected by administering to a subject a therapeutically effective amount of an oxidized phospholipid that is embraced by the general Formula of claim 1, but which is limited to compounds in which the oxidized moiety is either at position 2 or at both positions 1 and 2 of the glycerol backbone.

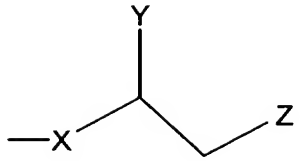
Specifically, new independent claim 20 recites a method of treating atherosclerosis and related diseases, including cardiovascular diseases, which is effected by administering to a subject a compound having the formula:



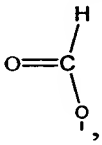
or pharmaceutically acceptable salts thereof, wherein:

(i) A_1 and A_2 are each independently selected from the group consisting of CH_2 and C=O, at least one of A_1 and A_2 being CH_2;

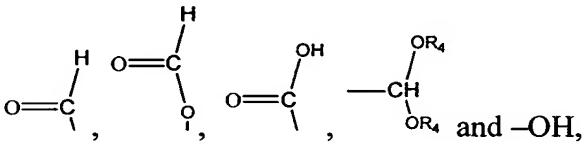
(ii) R_1 is selected from the group consisting of an alkyl chain having 1-27 carbon atoms and



wherein X is an alkyl chain having 1-24 carbon atoms, Y is selected from the group consisting of:

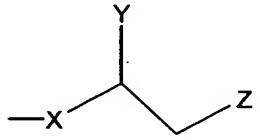
 , -OH, –H, alkyl, alkoxy halogen, acetoxy and aromatic functional groups; and

Z is selected from the group consisting of:

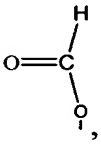


whereas R_4 is an alkyl;

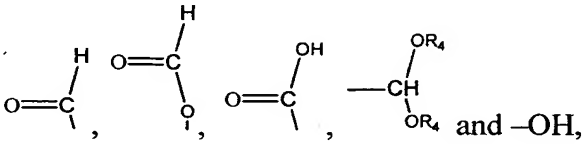
(iii) R_2 is



wherein X is an alkyl chain having 1-24 carbon atoms, Y is selected from the group consisting of:

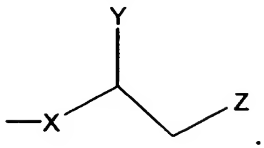
 , -OH, –H, alkyl, alkoxy halogen, acetoxy and aromatic functional groups; and

Z is selected from the group consisting of:



whereas R_4 is an alkyl; and

(iv) R_3 is selected from the group consisting of H, acyl, alkyl, phosphocholine, phosphoethanolamine, phosphoserine, phosphocardiolipin and phosphoinositol.

Independent claim 20 therefore pertains to compounds in which R_2 in the formula above is an oxidized moiety, represented by 

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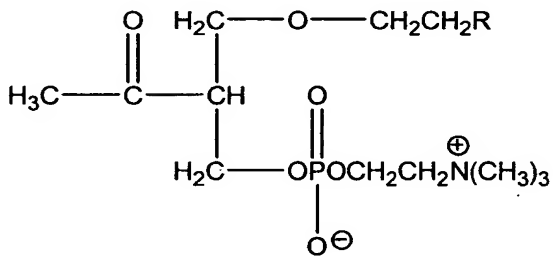
Applicant wishes to point out in this respect that Smal et al. disclose synthetic PAF analogs which are coupled to a protein carrier. The PAF analogs taught by Smal et al. include an oxidized moiety (i.e., an aldehyde) at the sn-1 position and an acyl moiety at the sn-2 position (see, for example, Figure 3 on page 717 of the reference).

As is well known in the art, PAFs are 1-alkyl-2-acetyl-sn-glycero-3-phosphocholines, naturally occurring ether-linked glycerolipids having the general Formula:



wherein R is an alkyl, typically having between 16 and 18 carbon atoms.

As is shown in the Formula above, in PAFs, the sn-2 carbon bears an acetyl moiety. In some well-known PAF analogs, this acetyl moiety may be substituted by a long chain acyl moiety (e.g., a fatty acid acyl). As is further well recognized in the art, and is also discussed in the instant application (see, for example, page 14, lines 23-26, and page 27), acyl moieties are highly susceptible to fast hydrolysis in biological systems, by phospholipase A_2 (see, for example, "A Textbook of Drug Design and Development", Povl Krogsgaard-Larsen and Hans Bundgaard, eds., Harwood Academic Publishers, chapter 13, pages 478-479, the paragraph bridging therebetween, and page 480, cloth d, which is enclosed herewith).

According to the teachings of Smal et al., PAF analogs that bear an oxidized moiety (i.e., aldehyde), are prepared by oxidizing an unsaturated alkyl chain present at the sn-1 position, thus providing a glycerophospholipid that is oxidized at that

position. Due to the instability of the PAF acyl moiety at the sn-2 position described above, oxidation of PAF analogs at that position is ineffective.

As is well studied in the art and is further discussed in detail in the instant application (see, for example, page 13, lines 1-23, and the references cited therein), the location of a chain bearing an oxidized moiety is known to affect the biological activity of a compound. In fact, as is also discussed in the instant application (see, for example, page 28, first paragraph), since in naturally occurring oxidized LDL derivatives the oxidized alkyl chain is typically located at the second position, preferred compounds according to the present invention include an oxidized moiety at the second position.

Hence, contrary to the teachings of Smal et al., preferred compounds according to the present invention include an oxidized moiety at the sn-2 position of a glycerophosphocholine. Furthermore, since the compounds of the present invention are not aimed at mimicking the platelet activating activity of PAF, the presence of an acyl moiety at the sn-2 position is not required.

Applicant therefore believes that since Smal et al. fail to teach the compounds recited in new independent claim 20, and further since the position of the oxidized moiety undoubtedly affects the biological activity of these compounds, as is argued hereinabove, the subject matter of new independent claim 20, as well as of claim 10-16 that depend therefrom, is not taught by Smal et al. nor by any of the other references cited by the Examiner in the outstanding Official Action.

It is therefore the Applicant's opinion that new claims 20-27 are neither anticipated nor rendered obvious by the prior art and are therefore allowable.

In view of the above amendments and remarks it is respectfully submitted that amended claim 1, claims 3-7, amended claim 8 and new claims 20-27 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

Date: December 13, 2005

Martin D. Moynihan,
Registration No. 40,338

Encl.:

1. Request for 2-month extension of time;
2. Additional Claim Fee; and
3. "A Textbook of Drug Design and Development", Povl Krogsgaard-Larsen and Hans Bundgaard, eds., Harwood Academic Publishers, chapter 13, pages 464-485.